REMARKS/ARGUMENTS

Claims 1, 4, 7-14, 21-29 and 32-85 are pending following entry of the present Amendment. The amendment to claim 1 finds support in the present application inter alia in the first paragraph under the heading "Brief Summary Of The Invention"

REJECTION OF THE CLAIMS UNDER 35 U.S.C.102

A. Claims 1, 22-28, 37-39, 45, 46, 72 and 73 are rejected over Malmberg [J.Am. Coll. Cardio. (1995) 26: 57-65]. Malmberg is cited as teaching the use of insulin-glucose infusion followed by multidose insulin treatment in diabetic patients with acute myocardial infarction for 3 months or longer where blood glucose in the infusion group is alleged (based on Table 3 of Malmberg) to be reduced from 15.4 to 9.6 mmol/l (corresponding to reduction from 232 mg/dL to 113 mg/dL according to the Office Action) to 8.2 mmol/l (92 mg/dL according to the Office Action) on hospital discharge. Thus, the blood glucose level in the patients in Malmberg is alleged to be reduced to between 92 and 113 mg/dL upon insulin infusion.

Applicant respectfully traverses this rejection.

In setting forth the above rejection, the Examiner is using an incorrect conversion factor in converting mmol/l of glucose to mg/dL of glucose. The correct conversion factor is that 1 mmol/l of glucose is approximately equal to 18 mg/dL of glucose (see page 16 of the present application and the Examiner's own citation to Table 1 of Malmberg as teaching a desired blood glucose level of 7-10.9 mmol/l or 126 -196 mg/dL of glucose).

Thus, using the correct conversion factor of 1 mmol/l of glucose to 18 mg/dL of glucose, Malmberg's Table 3 shows that infusion of insulin to Malmberg's patients results in a reduction of blood glucose from 15.4 mmol/l (= 277 mg/dL) to 9.6 mmol/l (= 173 mg/dL) to 8.2 mmol/l (= 148 mg/dL) of glucose; **i.e. reduction of blood glucose to between 148 to 173 mg/dL**. Accordingly, Malmberg cannot be held to anticipate the rejected claims.

B. Claims 1, 22-25, 27-29, 37-39, 45, 46, 72 and 73 are rejected over Shangraw [Metabolism (1989) 38:983-989]. Shangraw is cited as teaching the use of insulin infusion in

septic patients and patients with severe burn injury where the plasma glucose levels of patients is maintained between 80 to 120 mg/dL.

Applicant respectfully traverses this rejection.

The Shangraw study was designed to determine whether the insulin responsiveness of glucose and potassium metabolism is similar in septic patients and in burn patients who are not septic. There is no measure in Shangraw of the impact of insulin infusion on morbidity and/or mortality. Further, Table 1 and Figure 3 of Shangraw show that the plasma glucose levels in both sets of patients was about 110 mg/dL **before** treatment with insulin was initiated.

By comparison, the present amendment to claim 1 makes clear that the critically ill patient to be treated has a blood glucose level greater than 130 mg/dL and that the treatment then reduces the blood glucose level of the patient to between 60-130 mg/dL. Accordingly, withdrawal of this rejection over Shangraw is respectfully requested.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 103

Claims 1, 22-25, 27-29, 37-39, 45, 46, 72 and 73 are rejected over Case [Crit Care Nurs. (2000) Q22:75-89] in view of Gutierrez (US Patent 5,885,980). Case is cited as suggesting that insulin be administered to critically ill patients to maintain blood glucose at less than 200 mg/dL and Gutierrez as teaching that normal glucose levels are between 90 and 110 mg/dL. The Examiner therefore argues that one would be motivated by Case to lower the blood glucose levels of critically ill patients to a target range of 90-110 mg/dL as taught by Gutierrez because levels of 90-110 mg/dL are normal concentrations for treatment of diabetes.

With all due respect, Applicant disagrees.

Prior to the present invention, the opinion of the medical community was that hyperglycemia was beneficial in critically ill patients. For example in the Background Of Invention section (page 2, last paragraph) of the present application, it is disclosed that the standard practice of care for critically ill patients was to allow blood glucose levels as high as

250 mg/dL or above and that the reason for this practice was the thought that high levels of blood glucose are part of the adaptive stress responses and thus do not require treatment unless extremely elevated. In the reference cited to in connection with this statement [Mizock (1995) Am. J. Med 98:75-84], it is stated that in connection with critical care medicine: "modest degrees of hyperglycemia should be tolerated **without efforts to lower blood glucose to normal values of 90-120 mg/dL**"(emphasis added, page 82 of Mizock).

Mizock then states: "The level of glycemia should be high enough to maximize cellular glucose uptake without causing hyperosmolarity. A glucose concentration of 160 to 200 mg/dL has been recommended to achieve this goal and is probably acceptable to most clinicians".

Applicants submit that this teaching by Mizock of glucose levels of 160-200 mg/dL as recommended in critically ill patients, while consistent with the suggestion in Case that insulin be administered to critically ill patients to maintain blood glucose at less than 200 mg/dL, is completely contrary to the Examiner's assertion that prior to the present invention, one of ordinary skill in the art reading Case would be motivated to reduce blood glucose levels in critically ill patients to the normal levels of 90-110 mg/dL as taught by Gutierrez.

Rather, what the prior art teaches, **in the absence of hindsight afforded by the present application**, is that in the treatment of critically ill patients, one would not want to lower blood glucose levels to the range taught by Gutierrez; indeed, the prior art taught directly away from the claimed invention because the prior art taught that hyperglycemia in critically ill patients was beneficial.

Accordingly, this rejection is completely contrary to the accepted state of treatment of critically ill patients prior to the present invention and its withdrawal is respectfully requested.

In view of the above amendments and remarks, Applicant respectfully submist that the present application is in condition for allowance.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Please charge any deficiencies or overpayment to Deposit Account No. 14-1447.

Respectfully submitted,

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/Richard W. Bork, #36459/
Richard W. Bork, Reg. No. 36,459
Novo Nordisk, Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800

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